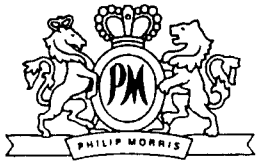

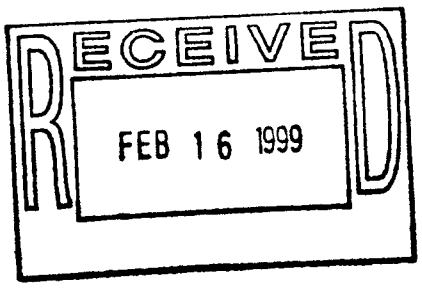

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Worldwide Scientific Affairs
P.O. BOX 25683, RICHMOND, VIRGINIA 23261-6583
February 12, 1999

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
79 Alexander Drive, Room 3217
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Dear Dr. Jameson:

Philip Morris takes this opportunity to respond to the call for final public comment on the possible listing of Environmental Tobacco Smoke (ETS) in the Report on Carcinogens, Ninth Edition, as noticed in *63 Fed. Reg.* 68783, December 14, 1998. We provide in these comments i) a review of the Draft Background Document for Environmental Tobacco Smoke, ii) a comparison between the Draft Background Document for ETS with the Draft Background Document for Diesel Exhaust, and iii) an examination of claims made by Mr. James Repace at the December 2, 1998, meeting of the NTP's Board of Scientific Counselors Report on Carcinogens subcommittee.

In our review of the Draft Background Document for ETS we identify a number of inaccuracies and omissions. Of concern is the omission of a large body of published literature on human exposure to ETS by K. Phillips and co-workers, and the IARC multi-center study described by Boffetta et al., in the Journal of the National Cancer Institute (**90**(19), October 7, 1998. We also address inconsistencies in the Draft Background Document discussion of various ETS components in our review. We question in some detail the considerable emphasis placed by the Draft Background Document on the 1992 US EPA report, which has been vacated in a judicial proceeding. We review data suggesting that a considerable reduction in relative risk is obtained by correction for several sources of potential systematic bias in the relevant epidemiological studies. We also note that many of the animal studies reviewed in the Draft Background Document did not adhere to Good Toxicological Practices, because they used inappropriate test material and an inappropriate experimental animal, the A/J mouse, which NTP had previously rejected (1986) for use in carcinogenicity testing. With respect to the application of the Bradford Hill guidelines to the epidemiological data, our review of the complete data set on reported ETS exposure and lung cancer demonstrates that the data are inconsistent, represent an extremely weak association, and are of questionable biological plausibility, due to low exposure levels of individual components.

We also submit a brief comparison of the Draft Background Document for ETS with the Draft Background Document for Diesel Exhaust, focusing on inconsistent treatment of the epidemiological data on these two substances, and how that treatment may have influenced the recent review by the RoC subcommittee. For instance, fourteen epidemiological studies of diesel exhaust were cited in the Draft Background Document for Diesel Exhaust, and the strengths and weaknesses each of the studies were reviewed. However, only four relevant studies (at least 30 have been published) were mentioned in the analogous section of the Draft Background Document for ETS, and no mention was made of any weaknesses in those studies. Also, in the Conclusions of the two Draft Background Documents, the authors make very different interpretations of very similar data.

In the last section of our submission, we review the relative risks derived by Mr. James Repace in both his written submission and public comments made on December 2. We demonstrate that Mr. Repace's theoretical models cannot, contrary to his statements, be verified by comparison to existing experimental data, and his suggestion that they can be is based on inappropriate assumptions regarding certain parameters in his models.

We believe that this commentary will be of value to your reviewers in their technical deliberations.

Sincerely,

Edward B. Sanders, Ph.D.
Group Director
Worldwide Scientific Affairs

Critique of NTP Draft Report on Carcinogens
Background Document for Environmental Tobacco Smoke
Dec. 2-3, 1998

Critique of NTP Draft Report on Carcinogens
Background Document for Environmental Tobacco Smoke
Dec. 2-3, 1998

As part of the National Toxicology Program's process for preparing the Ninth Report on Carcinogens, background documents reviewing relevant data on proposed compounds and processes were prepared. A critical review of the Background Document for Environmental Tobacco Smoke disclosed many serious deficiencies in accuracy, completeness, and objectivity in the papers discussed, and omissions of other relevant research. Details of these deficiencies are outlined below.

Physical and Chemical Properties

The Background Document on Environmental Tobacco Smoke (often referred to in this critique as the Background Document) defines Environmental Tobacco Smoke (ETS) as "the sum of sidestream smoke (SS) (interval between puffs), mainstream smoke (MS) emitted at the cigarette mouthpiece during inhalation, compounds diffused through the wrapper, and MS that the smoker exhales (NRC 1986; U.S. EPA 1992; CEPA 1997)." Despite this definition, the data presented in Table 1-1 and subsequently used as representative of ETS are mixed data for MS and/or SS smoke constituents. No data on the results of qualitative or quantitative analyses of compounds in ETS were provided, although relevant data have been published (Eatough et al., 1989; Heavner et al., 1995; Hodgson et al., 1996; Ogden and Maiolo, 1989). Exactly how well these mixed data on MS and SS composition support the claim on Page 1 of the Background Document for ETS regarding ETS composition:

> ETS contains more than 4,000 chemicals. Among these, at least 200 are toxic and 43 were known carcinogens as identified in the 1992 EPA review. Approximately 400 compounds have been quantified in both MS and SS smoke.

cannot be assessed.

The Background Document on ETS states on Page 3 that "Over 50 compounds in ETS have been identified as known, or reasonably anticipated to be, human carcinogens by various agencies (IARC 1986; CEPA 1997; NRC 1986; U.S. EPA 1992; RoC 1997: http://ehis.niehs.nih.
gov/roc/)." Most of these compounds are present in the particulate phase (IARC 1986)." Of these compounds, 40 are listed in Table 1-2 in the Background Document, and supporting data given for their occurrence in MS and/or SS. IARC (1986) actually presented limited data for ETS levels of nicotine, particulate matter, nine PAHs, two nitrosamines, acrolein, NO and NO_2 (a total of 15 compounds and particulate matter), but these data were not considered in the Background Document.

Also in the discussion of the properties of ETS, the Background Document for ETS simply categorizes various MS and/or SS components as "toxic". Use of this term is inappropriate in the absence of further details characterizing the situation surrounding exposure to a material.

Human Exposure

According to the Background Document for ETS, NIOSH estimated that nonsmokers are exposed to ETS equivalent to smoking 0.1 to 1.0 cigarettes a day (Millar, 1991). This claim is based on urinary adduct excretion, which, due to the absence of an appropriate biomarker, has not been typically used to assess ETS exposure; instead, this technique has been used to compare smokers to nonsmokers. In contrast, another cited study (Jenkins et al., 1996), reported that the calculated exposure was at least 10-fold lower.

An extensive body of published literature on human exposure to ETS has not been taken into consideration. Cities in which studies were conducted and the relevant reference include Barcelona (Phillips et al., 1997); Bremen (Phillips et al., 1998); Harrogate (Phillips et al., 1994); Kuala Lumpur (Phillips et al., 1998); Paris (Phillips et al., 1998); Prague (Phillips et al., 1998); Stockholm (Phillips et al., 1996); Sydney (Phillips et al., 1998); Turin (Phillips et al., 1997). These studies show that, based on a 90th percentile, the highest exposed subjects (those living in a smoking home and working in a smoking workplace) have considerably lower ETS exposures than stated above in the Background Document for ETS. Rather than the 0.1 to 1.0 cigarettes per day reported in the Background Document, exposures range from 4.6 cigarette equivalents per year (Kuala Lumpur) to 30.6 cigarette equivalents per year (Turin).

Tobacco-Specific N-Nitrosamines

Table 2-1 of the Background Document for ETS provides values for NNN, NAT and NNK levels in indoor air that were used to determine ETS exposure (Brunnemann et al., 1992; cited by Brunnemann et al., 1996). The ranges reported were none detected (ND) - 22.8 ng NNN/L, ND-9.5 ng NAT/L, and 1.4-29.3 ng NNK/L measured in 10 different environments. The units are incorrectly reported as ng/L rather than ng/m^3. This means the measured levels of the three TSNA in the various indoor venues were a thousand-fold less than indicated in Table 2-1. The cited Brunnemann et al. study calculated that, assuming a respiratory rate of 10L/min, 3.2-41 ng NNN and 2.5-43 ng NNK would be inhaled in a three hour period. In contrast, another study (Klus et al., 1992) not mentioned in the Background Document estimated a much lower maximum exposure of 10 ng/h total TSNA (NNN plus NNK) in indoor air of offices with poor ventilation.

The Background Document reports without attribution that "'Four nitrosamines (N'-nitrosonornicotine [NNN], N'-nitrosoanatabine [NAT], N'-nitrosoanabasine [NAB], and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK] have been associated with respiratory tract and pancreatic cancer." The only evaluations of the carcinogenicity of TSNA have been performed by the International Agency for Research on Cancer (IARC) Monograph 37, 1985) and they report the following:

NNN: 'There is sufficient evidence for the carcinogenicity of N-nitrosonornicotine to experimental animals.'
'No data on humans were available.'
The reviewed studies report major target organs to be:
Rat: Esophagus and nasal cavity
Hamster: Nasal cavity and trachea

Mouse: Lung
IARC Classification: 2B - Possibly carcinogenic to humans.

NAB: 'There is limited evidence for the carcinogenicity to N'-nitrosoanabasine to experimental animals.'
'No data on humans were available.'
The reviewed studies report major target organs to be:
Rat: Esophagus
Hamster: Inadequate for evaluation
IARC Classification: 3 - Unclassifiable as to carcinogenic to humans.

NAT: 'The available data are inadequate to evaluate the carcinogenicity of N'-nitrosoanatabine to experimental animals.'
'No data on humans were available.'
Rat: Not carcinogenic
IARC Classification: 3 - Unclassifiable as to carcinogenic to humans.

NNK: 'There is sufficient evidence for the carcinogenicity of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone to experimental animals.'
'No data on humans were available.'
The reviewed studies report major target organs to be:
Rat: Nasal cavity, lung and liver
Hamster: Nasal cavity, trachea and lung
Mouse: Lung
IARC Classification: 2B - Possibly carcinogenic to humans.

Subsequent to the reviewed studies, NNK has been reported to induce pancreatic tumors in rats when administered life-long in drinking water (Rivenson et al., 1988). Administration by other routes does not result in pancreatic tumors. Evaluations on carcinogenicity of the TSNA have not been made by other academic bodies or regulatory committee. For both NNN and NNK, the Environmental Defense Fund has concluded that missing data does not permit a National Safety Assessment.

The Background Document also claimed that since a biomarker study (Hecht et al., 1993) had reported that nonsmokers exposed to ETS absorb, retain, and metabolize NNK, TSNA levels were proposed as a monitor for ETS exposure. In the Hecht et al. study, nonsmokers were not exposed to ETS but were experimentally exposed to sidestream smoke on two identical occasions. The sidestream was generated from six machine-smoked Kentucky 2R1 reference cigarettes in a 16 m^3 room with limited ventilation (62 and 230 ug nicotine /m^3; 75 and 263 ng NNK /m^3). Clearly the artificial exposure concentrations for NNK in the Hecht et al. study differ dramatically from those reported for indoor air (Table 2-1; 1.4-29.3 ng/m^3 NNK).

Environmental Exposure

As mentioned above, only selected data on exposure to ETS were presented in the Background Document for ETS. The data summarized in Table 2-2 of the Background Document refer only to studies performed in the US, and make no mention of an extensive body of literature on human exposure to ETS published by Phillips et al. These studies again show that average ETS exposure is

considerably lower than reported in the Background Document. (See the **Human Exposure** section of this critique for references and values.)

Human Studies

Although the NTP background document briefly covers published studies that have investigated the possible association of ETS exposure with several cancer sites, the only site for which the evidence is judged to be "causal" is the lung. With respect to other sites the document states that

> Regarding other cancer sites, there is good evidence that ETS exposure is associated with nasal sinus cancer, and suggestive evidence for cervical cancer; available data do not support an association with bladder cancer; and the evidence is inconclusive regarding other sites and childhood cancer. (p. 46)

Therefore this discussion will be restricted to the evidence presented in the NTP document that claims to establish a "causal" relationship between reported ETS exposure and lung cancer.

Citation of Previous Reviews and Meta-Analyses

The NTP background document briefly discusses three previously published reports that have reviewed the evidence regarding possible associations between reported ETS exposure and lung cancer. The first is the 1986 IARC review on tobacco smoke (IARC, 1986). NTP correctly states the IARC review's conclusion, "that each study [reviewed by IARC] was compatible either with an increased risk or with the absence or risk." Furthermore, it was noted that IARC recommended that, "[a]s the estimated relative risks are low, the acquisition of further evidence bearing on the issue may require large-scale observational studies involving reliable measures of exposure both in childhood and in adult life." IARC clearly recognized the possible contributions that lack of reliable exposure measurements, smoker misclassification, and confounding by other risk factors could make to the very low observed relative risk, and not only recommended but undertook a large-scale multi-center case-control study of the possible association of reported ETS exposure and lung cancer. The results of this study were published in 1998 (Boffetta et al., 1998). Although it is true that this publication did not appear until October, 1998, it is nevertheless surprising that the NTP background document makes no mention whatsoever of the IARC results. This critique will not discuss the recent IARC results because a detailed analysis of the IARC study was previously submitted to the NTP (PM, 1998b). Also, it should be mentioned that despite the 1986 IARC report having stressed the importance of obtaining "reliable measures of exposure both in childhood and in adult life," the published study in 1998 contained no such measures of exposure.

The second review cited by NTP is the well known EPA report (U.S. EPA, 1992.) The EPA report was vacated by the United States District Court for the Middle District of North Carolina Winston Salem Division on July 17,1998, suggesting that citation of this report by NTP is inappropriate (*Flue-Cured Tobacco Cooperative Stabilizatiion Corp. et al. v. United States Environmental Protection Agency*, 4 F. Supp. 2d 435, (M.D.M.C. 1998). With its analysis of the stated bases for EPA's decision-making, the Court clearly called into question not only a number

of the conclusions reached by the EPA based on its analysis of the data, but also the methods by which EPA selected the data it reviewed.

First, the pooled relative risk utilized by the EPA was based solely on risk ratios or odds ratios for reported spousal ETS exposure and excluded results based on workplace and childhood exposure. The Court expressed concern over the EPA's exclusion of studies that failed to support its conclusions as follows:

> EPA's study selection criteria is disturbing. First, there is evidence that EPA "cherry picked" its data...Second, EPA's excluding nearly half of the available studies directly conflicts with EPA's purported purposes for analyzing the epidemiological studies and conflicts with EPA's Risk Assessment Guidelines (p. 460).

The Court ruled that "EPA disregarded information and made findings on selected information" (p. 466).

The NTP background document, however, seems to suggest that EPA did discuss other routes of exposure, since it states that, "[n]onsmokers with workplace or social exposure had a relative risk of 1.34 compared to nonsmokers with no ETS exposure, while nonsmokers with spousal as well as other sources of exposure had a relative risk of 1.59 compared to nonsmokers with no ETS exposure." However, these results are not derived from the EPA report. The EPA's epidemiological analysis was restricted solely to spousal smoking, and there is no information whatsoever in their analysis dealing with other exposure to other sources. The source of the numbers cited appears to be the Fontham study (Fontham et al., 1994), which EPA cites in Appendix A on page 40. Fontham reported a relative risk of 1.34 for occupational environments and 1.58 for social exposure.

Perhaps more importantly, the Court questioned EPA's classification of ETS as a Group A carcinogen because of the extremely weak association upon which it was based. The Court stated:

> EPA's conduct raises several concerns besides whether a relative risk of 1.19 is credible evidence supporting a Group A classification. First with such a weak showing, if even a fraction of Plaintiff's allegations regarding study selection or methodology is true, EPA cannot show a statistically significant association between ETS and lung cancer (p. 462).

The Court's decision contains two statements from EPA staff that also clearly call into question EPA's classification decision. Again, citing the Court:

> Acting Director [EPA Environmental Criteria and Assessment Office] Chris DeRosa advised EPA that the evidence "support[ed] the conclusion that ETS be classified as a Group B1 carcinogen" (p. 458).
>
> EPA Toxicologist Larry Glass concluded, "it is recommended that the [epidemiological] evidence be summarized as being limited...This would classify ETS into a weight-of-the-evidence Group Be [*sic*, B1]" (p. 458).

All of the above strongly suggests that a conclusion that ETS exposure is causally linked to lung cancer cannot be based solely on the EPA report.

The third review cited by the NTP background document is the California EPA report (CEPA, 1997). The very brief reference to California EPA simply states that five studies published after the US EPA (1992) were reviewed by California EPA, that these studies addressed many of the criticisms of previous studies, and that the results of these studies were consistent with the US EPA report finding of a 20% increase in lung cancer among non-smoking women associated with reported ETS exposure. Since the NTP background document itself reviews four of these five studies, further discussion will be deferred.

Current Epidemiological Studies

NTP begins this section by referencing Table 3-1 (pp. 32-43), which gives some brief information regarding epidemiological studies of reported ETS exposure and cancer published since the 1986 IARC report. The Background Document claims that this table includes for adults 10 cohort studies, 3 of which had lung cancer as the endpoint. Inspection of the table indicates only six cohort studies, one of which is incorrectly identified. There are also listed 15 case-control studies investigating the possible association of ETS exposure and lung cancer. In actuality there have been about 35 epidemiological studies since the 1986 IARC report was published (Hackshaw, et al., 1997). As a consequence there are many studies which have not been reviewed by NTP, and they provided no explanation for the omissions.

NTP focuses specifically on four studies published since EPA, three case-control studies and one cohort study. The first of these studies is Brownson, et al. (1992). The sole risk estimate cited by NTP from this study is an odds ratio (OR) of 1.3 (95% CI, 1.0-1.7) for >40 pack-years of exposure. The background document does not cite the overall OR of 1.00 (95% CI, 0.80-1.20), which characterizes the study as a whole and suggests no association between reported ETS exposure and lung cancer. Moreover, reported OR's for 1-15 pack-years and 16-40 pack-years of exposure were 0.9 and 0.8 respectively. It should be noted that these data are for reported exposure from all household members. The corresponding OR's for reported spousal exposure, the only exposure source which can be used to compare this study with others, are 1.0 (95% CI, 0.8-1.1) for the total sample, and 0.7, 0.7 and 1.2 for 1-15 pack-years, 15-40 pack-years, and >40 pack-years, respectively. No significant association was reported for childhood exposure, as was mentioned in the Background Document, or for workplace exposure, a point not mentioned by the Background Document.

The second study on which the NTP background document focuses is Stockwell, et al. (1992). For this study, the OR for adult exposure is cited as 2.4 (95% CI, 1.1-5.3) for 40+ smoke years of reported exposure, where smoke years is the cumulative sum of years smoked by all family members. Once again, NTP does not provide the OR for the entire sample, which is 1.60 (95% CI, 0.80-3.00). The NTP document also cites an OR of 2.4 (95% CI, 1.1-5.4) for 22+ smoke years reported exposure in childhood. The overall OR for childhood exposure was 1.70 (95% CI, 1.00-2.90). Moreover, the majority of studies which have investigated the possible association for reported childhood ETS exposure and lung cancer are not statistically significant, and many report OR's of less than 1.0 (see, for example, Bofffetta, et al., 1998). Therefore, not only has the NTP chosen to report an

elevated OR, reporting only the result at the highest dose, but by doing so suggested to the reader that there is an association where the overall OR suggests none exists. Lastly, it should be noted that Stockwell failed to find a statistically significant increase in risk for reported exposure either in the workplace or in social situations; however, no numerical risk data are presented in the study. Neither of these findings was reported in the NTP background document.

The last case-control study focused on by NTP is the Fontham, et al. study (1994). Here again, only OR's reported for the highest doses are presented. For spousal exposure an OR of 1.79 (95% CI, 0.99-3.25) for 80+ pack-years of exposure was cited, as compared to the overall OR of 1.29 (95% CI. 1.04-1.60). The OR's as a function of number of pack-years of reported exposure are, 1.00 (unexposed), 1.08 (1-15 pack-years), 1.04 (16-39 pack-years), 1.36 (40-79 pack years), and 1.79 (80+ pack years). The OR cited for occupational exposure was 1.86 for >30 years exposure. The overall OR is 1.39 (95% CI, 1.11-1.74). The dose-response trend for years of reported exposure is statistically significant. Lastly, NTP cites an OR of 1.54 (95% CI, 0.93-2.54) for >30 years exposure. Here, the difference is slight, since the overall OR for social exposure is 1.50 (95% CI, 1.19-1.89).

It is at best unusual that the NTP background document cited only selected OR's for the three case-control studies cited above. First of all, it is not generally accepted practice for epidemiological studies to report the results only for the highest dose. This is the case because the results at the highest dose comprise only a part of the total case group, and sometimes a very small part. For example, for Brownson, et al. the highest exposed group (40+ pack-years of exposure) was 26.7% of the total sample (146 out of 546 total cases). For Fontham, et al. the percentage of the highest exposed group (80+ pack years of exposure) was only 3.9% (24 out of 611). Stockwell, et al. do not provide information on the size of the group for which they report the highest exposure (40+ smoke years); however, they indicate that their three groups were "subdivided into three categories of approximately equal size for both early and adult years." Therefore, not only are the random errors considerably greater for the highest exposed group compared to the total sample, but the highest exposed group is that group that is most likely to be affected by differential recall bias (CRS, 1995). It is therefore necessary to report results for both the complete sample and for any sub-samples subdivided by level of exposure. Secondly, the casual reader could be misled by seeing only the results for the highest exposed group. OR's of 1.3, 2.4, and 1.79 suggest a much higher risk than do 1.0, 1.6, and 1.29. Lastly, it is important to point out that a toxicologist might interpret NTP's practice as an attempt to follow the normal protocols for carcinogencity testing in animals; namely, to use the highest tolerated dose. However, using epidemiological data in this manner is not at all appropriate, since there is no possible manner in which the level of exposure can be controlled or even accurately determined.

The cohort study discussed in the NTP document was published by Cardenas, et al. (1997). The NTP report points out that Cardenas et al. reported a weak apparent association with reported spousal ETS exposure for women, RR = 1.2 (95% 0.8-1.6) but not for men. However, the Background Document for ETS also notes that a positive trend in risk was reported for women with increasing number of cigarettes smoked per day by the spouse ($p = 0.03$) and for pack-years of exposure ($p = 0.1$). The latter dose-response trend, however, is not statistically

significant, which is apparent from inspection of the relative risks: 1.0 (no exposure), 1.0 (1-16 pack-years of exposure), 1.5 (17-35 pack-years of exposure), and 1.5 (36+ pack-years of exposure).

As pointed out above, Table 3.1 provides brief information on 3 cohort studies and 15 case-control studies which have investigated the possible association of spousal ETS exposure and lung cancer published since 1986. One of the studies, listed as a cohort study in the table, is by Pershagen, et al. (1987). This study, however, was a case-control study, not a cohort study. In addition NTP's summary of the study's findings could clearly result in some misinterpretations. The overall OR for all lung cancer cell types combined was 1.2 (95% CI, 0.7-2.1). The OR of 3.3 reported for squamous cell or small cell carcinoma was based on a total of 20 cases, an extremely small number for a case-control study. The statistically significant dose-response trend mentioned in the table is based on two groups characterized as "low exposure" and "high exposure." There were only 3 cases in the "high exposure" group. Given the uncertainty of the exposures, the possibility of differential recall bias, the fact that the analysis was based on only two points, and the large random error in the "high exposure" group (OR = 6.4 (95% CI, 1.1-34.7), the simple statement, with no accompanying caveats, that a significant dose-response trend was observed could lead to misinterpretation of the data.

Discussion of Potential Systematic Biases

The NTP document points out that a number of possible systematic biases have been proposed to account for the reported small increase in risk for lung cancer associated with ETS exposure. The Background Document specifically mentions a number of these; namely, selection bias in hospital-based studies; misclassification of non-lung cancers as lung cancer; misclassification of former or current smokers as non-smokers; misclassification of the extent of ETS exposure in studies using surrogate respondents; and, confounding by dietary factors or occupational exposures. The document then contends that, "[a]ll of these issues are addressed by three recent large population-based studies (Stockwell, et al., 1992; Brownson, et al., 1992; and Fontham, et al., 1991, 1994)." This statement is not supported by the facts.

The three studies cited above were reasonably designed studies that attempted to minimize at least some possible systematic biases. It would appear that these studies attempted to minimize possible problems resulting from either selection bias or misclassification of non-lung cancers as lung cancers. However, it should be noted that the overall OR's for the three spousal studies were 1.0, 1.29, and 1.60 suggesting that despite the effort with which these studies were carried out, there is a great deal of variability in the results. Moreover, these studies have not eliminated either confounding or misclassification of former or current smokers as non-smokers.

No effort was made by either Brownson, et al. or Stockwell, et al. to eliminate misclassification of smokers, occasional or regular. Fontham, et al. on the other hand obtained information on smoking habit from the medical records, from the attending physician, and from case interviews. However, one might assume that an individual who had decided to misrepresent smoking status on one occasion might continue to do so. It would have been of interest had Fontham, et al.

presented data indicating the consistency of the information obtained from the three different sources, but no such data were provided.

The most frequently cited "proof" obtained by Fontham, et al. is based on urinary cotinine/creatinine ratios. Urine samples were obtained at the time of interview from 356 cases and from 1064 controls. Cotinine/ creatinine ratios indicative of possible smoking (>100 ng/mg) were found in only 0.6% of cases, which has been claimed to demonstrate that misclassification of smoking cannot possibly be an important factor. However, this is not at all the case for three reasons. First, cotinine levels reflect current smoking only and do not reflect past smoking history. Secondly, once an individual has been diagnosed as having lung cancer, that individual is likely to stop smoking (and perhaps deny ever smoking). Thirdly, many of these interviews most likely occurred within the hospital where smoking would not have been allowed. That this is almost certainly the case is borne out by the fact that 2.3% of the controls had cotinine/creatinine ratios greater than 100 ng/mg. A finding of a 2.3% misclassification rate for the cases would have led to a lowering of the excess risk reported by Fontham, et al. by between 10 and 25 % irrespective of the level found for the controls.

Given the strong statistical association of active smoking with lung cancer, it is much more likely for there to be a higher percentage of misclassified smokers in the case group than in the control group. Further discussion by NTP on misclassification cites references by Riboli, et al. (1995), Nyberg, et al. (1997), and Wells, et al. (1998a). The Nyberg, et al. and Wells, et al. references are not in substantive disagreement with the conclusion by Wald, et al. (1986) that about 7% of ever smokers would be misclassified as never smokers. (Also, see Lee and Forey (1996) for an exhaustive review of this subject that comes to a similar conclusion.) The Riboli, et al. analysis, however, would suggest that only 1.5% of their sample were "covert smokers." Of a total of 27 women with cotinine/creatinine levels between 50 and 150 ng/mg, 16 reported high ETS levels. Therefore, Riboli, et al. set the cut-off point at 150 ng/mg leaving a total of 20 women, or 1.5%, who were considered to be misclassified smokers. One would assume, however, that if 16 of the 27 women interviewed claimed to have been exposed to high levels of ETS, the remaining 11 did not make this claim. Therefore, it would seem more reasonable to assume that a total of 31 women, or 2.2%, were smokers misclassified as never smokers. This number actually is in close agreement with the findings of Fontham, et al. for their control group. Also, it is important to note that the Riboli, et al. study, although providing some information on misclassified current smokers, provides no information on misclassified former smokers.

The NTP document concludes its discussion of misclassification by stating that, "[t]hus it appears unlikely that misclassification of former or current smokers as nonsmokers can explain the association of lung cancer with ETS exposure." However, adjustment for misclassification of smokers as never smokers can at a minimum lead to a decrease of 0.05 in the relative risk, or about 25% of the observed increased risk. Therefore, to discount it entirely, simply because it does not explain all of the increased risk, is not at all justifiable.

The other bias that the three case-control studies cited allegedly address is confounding. The NTP document points out that Fontham, et al. adjusted for a large number of potential confounders (age, race, study area, education, diet, family history of lung cancer, and employment in high-risk occupations) with no change in the reported OR (increase from 1.27 to 1.29). To suggest that the results from a

single study prove that confounding has no influence on the reported increase in excess risk is simply not good epidemiology. For example, for the Schwartz, et al. study (Schwartz, et al., 1996), a relatively large (185 cases), recent, American case-control study, the covariant adjusted OR is 1.10 (95% CI, 0.72-1.68) compared to an unadjusted OR of 1.18 (95% CI, 0.77-1.81). Therefore, based on this single study, one would have concluded that adjustment for confounding resulted in a decrease of 44% in the reported excess risk. Clearly, all of the studies need to be examined. One way to do this is to compare a meta-analysis of data adjusted for confounding where possible, with a meta-analysis for the same studies using unadjusted data. When this is done for studies published through March, 1997, the results, for purposes of comparison of confounding only, are an adjusted RR of 1.16 (95% CI, 1.09-1.25) compared to an unadjusted RR of 1.19 (95% CI, 1.11-1.28). Although this difference might appear small, it does represent 16% of the risk being discussed. Given that most of the studies analyzed looked at only a small number of confounders, it is highly likely that, had adjusted OR's been calculated using a more comprehensive list of confounders, the difference would have been greater. In any event, confounding together with misclassification can explain about 40% of the excess reported risk.

The NTP document fails to address one of the most important sources of potential bias; namely, differential recall bias (Congressional Research Service, 1995). This bias is derived from the fact that cases, who may be searching for an explanation for their disease state, are far more likely to recall ETS exposure than are controls. This is particularly the case for the small number of cases who make up the highest reported exposure group. The potential contribution that differential recall bias could make to the observed relative risks was first pointed out in the CRS report (1995). The fact that the NTP document fails to even mention this potential bias is a glaring omission. NTP does, perhaps, address differential recall bias implicitly. It points out that the results from the case-control studies were supported by Cardenas, et al. (1997), a cohort study. Cohort studies are not subject to differential recall bias, since smoking histories are obtained at the start of the follow-up period. As pointed out above, Cardenas, et al. reported an adjusted RR for women of 1.2 and an adjusted RR for men of 1.1, which, although not statistically significant, could be argued to be consistent with various meta-analyses. However, it is perhaps of great significance that Cardenas, et al. reported at best weak evidence of a dose-response trend. If this critique were to take the position that a single study represents positive proof of a hypothesis, as the NTP background document frequently does, one could then state that Cardenas, et al. establishes the fact that the positive dose-response trends reported for case-control studies are the result of differential recall bias.

Workplace Exposure

The NTP background document devotes only a single paragraph to workplace exposure. They point out that a meta-analysis carried out in 1994 (LeVois and Layard, 1994) gave a pooled relative risk of 1.01, and that this meta-analysis has often been cited as establishing the absence of an association of workplace ETS exposure with lung cancer. NTP points out, however, that Wells (1998b) recently published a meta-analysis that reported a pooled relative risk of 1.39 (95% CI, 1.15-1.68). Wells arrived at this result by excluding most of the studies that have been published on the possible association of reported workplace ETS exposure and lung cancer. Without going into a discussion of the appropriateness of excluding three-quarters of all studies and of his selection

criteria, it is clear that what Wells has done is to arrive at a result that is dominated by a single study; namely, Fontham, et al (1994). Moreover, instead of using the OR of 1.39 (95% CI, 1.11-1.74) published in 1994, Wells uses an OR of 1.56 from the Fontham group found in a letter to the editor (Reynolds, et al., 1996). The upwards revision to the OR apparently reflects the inclusion of additional confounders, and the exclusion of a small number of women who had worked for less than 6 months. The effect of adjustment for confounders on the workplace OR for Fontham, et al. seems totally inconsistent with all other results. The unadjusted OR in the 1994 publication was 1.12 (95% CI, 0.91-1.36). This value is adjusted upwards first to 1.39 in the 1994 publication and then to 1.56 in a non-peer reviewed commentary. With only four small studies to counterbalance this result, it is not surprising that Wells' pooled relative risk is as high as it is.

Wells (1998b) also presents a meta-analysis including all published studies, which results in a pooled relative risk of 1.19 (95% CI, 1.04-1.35). The disparity between this result and those of earlier meta-analyses, including that of LeVois and Layard, is not the consequence of "inclusion of seriously flawed studies and incorrect heavy weights assigned to relative risks less than unity" as stated in the NTP background document. No studies were included in the LeVois and Layard meta-analysis that were not also included in the complete meta-analysis performed by Wells. There have been studies published since LeVois and Layard, which lead to an upward revision. In addition, Wells used three OR's which were higher than those in the originally published literature, for two of which there is considerable justification, and corrected an error relating to the confidence limits for another study that had also been incorrectly published in the original paper. The implications made by the NTP document regarding the quality of the studies included by LeVois and Layard and weight assigned by LeVois and Layard to relative risks less than unity are completely incorrect and completely unwarranted.

The finding of a pooled relative risk for workplace exposure that is essentially equal to the pooled relative risk for spousal exposure raises a fundamental question regarding the meaning of Wells' interpretation of the epidemiological data. As the NTP background document itself points out, "[m]easurements of cotinine in nonsmokers indicate that that (sic) spousal smoking contributes more exposure than workplace smoking... (Pirkle et al., 1996)." This conclusion is amply confirmed by the publication of a number of recent studies which have measured the actual exposure to ETS in a number of settings and have found that in "smoking homes," exposure to ETS-derived RSP and nicotine is almost 10-fold greater than in "smoking workplaces" (see, e.g., Jenkins (1996) and Phillips (1996)). If NTP accepts the contention that spousal exposures are greater than workplace exposures, it is not logical for NTP to also accept the contention that the epidemiological risks for the two are equivalent. This is another example, others having been pointed out in previous submissions to the NTP, of assuming that extremely weak epidemiolgical point estimates—such as the reported data for both spousal and workplace ETS exposure—are actually meaningful.

Discussion of Human Studies

The NTP background document concludes that, "it appears unlikely that either confounding or other types of bias can account for the risk ascribed to ETS exposure. The consistency of risks observed across individual studies conducted with various populations and methodologies, the presence of an exposure-response relationship in many studies, and the biological plausibility of the relationship all

argue strongly that the association of ETS exposure is causal." Thus the NTP background document purports to utilize three of the Bradford Hill (1965) guidelines - consistency, dose-response, and biological plausibility - to establish a "causal" relationship between reported ETS exposure and lung cancer. It is important to note that there are some serious concerns as to the appropriateness of applying the Bradford Hill guidelines to these data. No single study has ever adequately controlled for all possible confounders, and it is not at all clear that such a study could ever have been conducted. By the same token, no study has ever properly evaluated exposure. Therefore, to apply any type of criteria to clearly incomplete data in order to assess possible "causation" is not likely to be a meaningful exercise, particularly when the strength of the association is weak (see below). Nevertheless, it must be recognized that virtually all epidemiological studies suffer from these weaknesses, and that it is currently standard practice to attempt to assess "causality" despite this. Therefore, in attempting to apply the Bradford Hill guidelines to the epidemiological data for ETS exposure and lung cancer, the NTP is simply following current practices. The question that remains is, has the NTP appropriately applied the Bradford Hill guidelines in order to arrive at its opinion that the association of ETS exposure with lung cancer is "causal"? Therefore, it is important to carefully examine those guidelines that the NTP has selected as well as one very important guideline that NTP failed to mention.

One of the most important of the Bradford Hill guidelines for causation—and one not cited by the NTP– is strength of the association. Clearly, the strength for the association of reported ETS exposure and lung cancer is extremely weak, and were one to base an analysis of "causality" only on the strength of the association, the conclusion would be that the reported association is not "causal" (Taubes, 1995). Nevertheless, if one can demonstrate that this very slight increase in risk can not be attributed to systematic biases, then the association may indeed be real. It is certainly possible that no single bias can account for all of the reported increase in risk in some of the studies. Nevertheless, as has been pointed out above, a conservative estimate of the effects of only two biases, smoker misclassification and confounding, can account for about 40% of the reported excess risk. Thus, the relative risk becomes about 1.11. There are other biases, not yet thoroughly examined, such as differential recall bias, improper matching of cases and controls, and interviewer bias, which could easily explain this residual effect.

The second guideline used by NTP is consistency. Bradford Hill (1965) defines consistency as obtaining similar results from studies carried out by different investigators in different locations. The epidemiological results for the association of ETS and lung cancer are consistent, however, only when multiple studies are pooled together. For example, the reported spousal ORs in the three case-control studies discussed in the NTP background document were 1.0, 1.29, and 1.6. These results do not appear to be consistent. Moreover, if one looks at the recently published results from the IARC multi-center study (Boffetta, et al., 1998), the individual center results vary from an OR of 2.29 in Stockholm to 0.72 in France. Yet these results were obtained by methodologies designed to be as similar as possible, which was clearly not the case for Brownson, et al., Stockwell, et al., and Fontham, et al..

The third guideline cited is the presence of dose-response trends in many studies. While several case-control studies have reported a dose-response, it is well known that case-control studies can be significantly affected by differential

recall bias. Although there is little information in the literature that can document the potential effect of differential recall bias, a recent study by Nyberg, et al. (1998) provides sufficient data, based on next-of-kin interviews, to suggest its possible importance. Nyberg, et al. found that there were a small number of individuals in both the case and control groups whose claim of high exposure to ETS was not confirmed by next-of-kin. The authors actually used the fact that the number where such a disagreement was noted was small as substantiation for the lack of effect for differential recall bias. However, when the OR's as a function of "dose" are recalculated, the apparent dose-response trend essentially disappears. (See PM, 1998c) It is also worthwhile to note that disagreement as to extent of exposure between subjects and next-of-kin occurred only for the highest exposed group. As pointed out above, the lack of a dose-response trend with respect for almost all metameters for the cohort studies published on ETS exposure and lung cancer that are either large enough or sufficiently well conducted to be relied upon (Cardenas, et al., 1997; Garfinkel, 1981) also suggests that differential recall bias could be playing a major role with respect to the reported dose-response trends in case-control studies.

The last guideline used by the NTP background is biological plausibility. This guideline, of course, does not depend on the epidemiological data. However, if biological plausibility is to be depended on, then an extrapolation of dose from active smoking should be consistent with the reported epidemiological pooled relative risk. Such is not the case (Scherer and Heller, 1998). Contending that biological plausibility can be used in a qualitative manner to support a "causal" association of ETS exposure and lung cancer, but not in a quantitative manner, the EPA utilized epidemiological data to attempt to quantify the "risk" posed by ETS exposure. The EPA report points out:

> The rapid dilution of both SS [sidestream smoke] and exhaled MS [mainstream smoke] into the environment and changing phase distributions of ETS components over time raise some questions about the carcinogenic potential of ETS under actual environmental exposure conditions. Furthermore, while MS and ETS may be qualitatively comparable, active smoking data do not constitute a good basis for quantitative estimation of the health effects of passive smoking because the relative uptake and deposition between active and passive smokers of the agent(s) responsible for these effects are not known... (page 4-29)

The EPA's on-again, off-again attitude to biological plausibility was a point that was clearly emphasized in the US District Court's decision that vacated the EPA report.

> Since Chapter 2 found ETS and MS not sufficiently similar, Chapter 3 found them similar, and Chapter 6 found them dissimilar, EPA apparently used a different risk assessment methodology for each chapter. The court is faced with the ugly possibility that EPA adopted a methodology for each chapter, without explanation, based on the outcome sought in that chapter.

Moreover, biological plausibility also suffers from the fact that the vast majority of all compounds derived from the combustion of tobacco are derived from the combustion of all organic matter, and that these compounds are found in measurable amounts in indoor air whether smoking is taking place or not.

Studies of Cancer in Experimental Animals

The Background Document did acknowledge (Section 4.1.1, p. 47) that, prior to the IARC 1986 Report, exposure of laboratory animals to tobacco smoke by inhalation had not resulted in increased incidences of lung tumors per se in rats, mice, rabbits and dogs.

Exposure of laboratory animals to tobacco smoke by the inhalation route

The Background Document for ETS selectively reports a series of studies (Witschi et al., 1995, 1997a, 1997b) published since the IARC 1986 Monograph in which strain A/J mice were exposed using various experimental protocols to sidestream cigarette smoke, or a mixture of sidestream smoke and mainstream smoke, as a surrogate for ETS. None of these studies actually evaluated the appropriate test material, namely ETS. ETS is not equivalent to sidestream or mainstream smoke (Lofroth et al., 1989; Haussmann, et al., 1998a), and a mixture of both sidestream and mainstream smoke does not constitute ETS since aging, dilution and removal of some smoke components by smokers prior to exhalation of mainstream smoke are not accounted for in the surrogate test material. Aging and dilution are the major conditions that differentiate true ETS from the examined test material (Baker and Proctor, Environ. Int., 16, 231-245, 1990). The Background Document for ETS also referred to an inhalation study (Finch et al., 1996) which was based on mainstream smoke exposure. No further discussion of this study will be presented here because mainstream smoke cannot be used as a surrogate for ETS.

Good toxicological practice for inhalation studies should include a full chemical characterization of the test material, an assessment of the particle size distribution, and (ideally) measurement of respiration rates in the study animals (Montesano, et. al, 1986) or the use of appropriate biomonitoring measures. These measures are required to confirm that inhalation of the test material occurred, and to define the actual inhaled dose. Additional care is required to ensure that non-inhalation routes of administration (dermal, oral from preening) are minimized. The latter can only be avoided in nose-only exposure to the test material. The studies reviewed in the Background Document for ETS failed to use the appropriate test material (ETS), provided little or no characterization of the test material and particle size distribution, failed to adequately confirm that inhalation had occurred following whole-body exposure to the test material, and did not assess the proportion of test material taken up via inhalation relative to non-inhalative routes. The latter is relevant for smoke inhalation studies, since the uptake of nicotine was determined to be two- to -three-fold higher in rats exposed under whole-body as compared to nose-only conditions to an ETS surrogate (Haussmann et al., 1998b).

A number of studies using aged and diluted sidestream smoke, a more appropriate surrogate test material for ETS, were also either not reviewed or ignored in the Background Document . These studies include:

1. A 90-day study using both rats and hamsters, using a single 4 mg/m^3 TPM concentration and 10-h exposures (von Meyerinck et al., 1989).

2. A 12-month study using rats with three exposure concentrations (0, 6.0 and 12.0 mg/m^3) and 7- or 12-h exposures comparing the whole-body and nose-only exposure modes (Haussmann et al., 1998b).

3. A 90-day study using rats with four exposure concentrations (0, 0.1, 1.0 and 10.0 mg/m^3) and 6-h exposures (Coggins et al., 1993).

4. A 90-day study using rats with three exposure concentrations (0, 6.0 and 8.7 mg/m^3) and 6-h exposures comparing fresh and room-aged sidestream smoke (Haussmann et al., 1998a)

5. A 14-day study in rats with four exposure concentrations (0, 0.1, 1.0 and 10.0 mg/m^3) and 6-h exposures (Coggins et al., 1992).

6. A 6-month study in the A/J mouse, using a single 4 mg/m^3 TPM concentration and 6-h exposures (Pinkerton et al., 1996).

Taken as a whole, these studies only reported adaptive, reversible changes at highly exaggerated concentrations of the test material. The changes did not progress from short to chronic exposure. In addition, the chronic rat inhalation study did not show any dysplastic or neoplastic changes (Haussmann et al., 1998b). It should be noted that Studies 2, 3, 4, and 5 were noted in prior submissions to the NTP.

Ignoring many available studies, the Background Document for ETS relied completely on the selected studies (discussed in the following paragraphs) from the University of California at Davis which employed the A/J mouse. The A/J mouse strain is known to have a high incidence of spontaneous lung tumors which occur at a rate of 0.21 tumors/mouse at 24 weeks, but may be found as early as 3-4 weeks of age, with a steady increase to almost 100% by 24 months of age (Shimkin and Stoner, Adv. Cancer Res., 21, 1-58, 1995).

Witschi et al. (1995) exposed male strain A/J mice to smoke from the Kentucky 1R4F reference cigarette (4.1-4.5$\pm$0.4-0.6 mg TPM/m^3, 17$\pm$2 ppm CO) for 6 h/d, 5 d/wk for 6 months. The Background Document notes that the authors report that after 6 months, tumor incidence in all animals (0.42$\pm$0.64 in 'smoke-exposed' and 0.39$\pm$0.60 in 'air control' mice) and tumor multiplicity (1.25$\pm$0.45 in 'smoke-exposed', and 1.07 $\pm$ 0.39 in 'air-control' mice) were not statistically different. No mention was made of the fact that, 'air-control' animals still showed a 33% tumor incidence indicating the high spontaneous rate of lung tumors in this mouse strain.

Witschi et al. (1997a) exposed male strain A/J mice to smoke of the Kentucky 1R4F reference cigarette (87.3$\pm$21 mg TPM/m^3, 244$\pm$140 ppm CO) for 6 h/d, 5 d/wk for 5 months. Animals were not exposed to sidestream smoke as reported in the Background Document, but to a mixture of 89% SS and 11% MS. Again, adherence to Good Toxicological Practices (Montesano, et al., 1986) would have led to rejection of the study results showing association between exposure and tumor multiplicity due to overt toxicity (absolute reduction in body weight of the 'smoke-exposed' mice up to 16% compared to the start of the exposure). The OECD guideline no. 451 (1981) for the evaluation of chemicals for carcinogenicity recommends that the reduction in body weight gain not exceed 10% in order to be acceptable for regulatory purposes. Thus, the conditions of this study were far beyond those normally considered appropriate for regulatory decision-making. The

Background Document states that the authors report that after 5 months, tumor incidence in all animals (6/24 in 'smoke-exposed' and 2/24 in 'air-control' mice) and tumor multiplicity (1.2±0.2 in 'smoke-exposed and 1.0±0.0 in 'air-control' mice) were not statistically different, but after 4 months recovery in filtered air, tumor incidence in all animals (20/24 in 'smoke-exposed' and 9/24 in 'air-control' mice) and tumor multiplicity (1.7±0.2 in 'smoke-exposed' and 1.3±0.2 in 'air-control' mice) were statistically different. Studies performed in parallel using butylated hydroxytoluene, an agent known to enhance lung tumor development in mice, essentially failed to statistically significantly influence tumor incidence or multiplicity. Also, the growth of urethan- or 3-methylcholanthrene-induced lung tumors in A/J mice could be significantly suppressed as long as the animals were exposed to "ETS." Increased cell proliferation was only reported for the first six weeks of inhalation and not thereafter.

Witschi et al. (1997b) exposed groups of female strain A/J mice to 'whole smoke' of the Kentucky 1R4F reference cigarette (78.5±12.4 mg TPM/m^3, 211±24 ppm CO) for 6 h/d 5 d/wk for 5 months, and to 'filtered smoke' of the Kentucky 1R4F reference cigarette (0.1±0.2 mg TPM/m^3, 113±23 ppm CO) for 6 h/d, 5 d/wk for 5 months. As in the previous Witschi sutdy (1997a), the test material was a mixture of 89% SS and 11% MS. (The CO concentrations were incorrectly stated in the Background Document as 23 ± 2 ppm CO for both 'whole smoke' and 'filtered smoke'.) The Background Document stresses that tumor incidence and tumor multiplicity in 'filtered smoke' exposed animals were numerically (but not statistically) greater than in air control mice after 5 months. However, after recovery in air for 4 months, tumor multiplicity was significantly greater in 'whole smoke' and filtered smoke exposed animals than in air controls (Table 4-9). Traditionally, the A/J mouse pulmonary tumor bioassay is considered positive when there is a statistically significant increase in the incidence of tumor-bearing mice as well as a statistically significant increase in tumor multiplicity, with the latter carrying more weight (Maronpot et al., 1983). In animals exposed to either 'whole smoke' or 'filtered smoke' for 5 months and allowed to recover in air for 4 months, only lung tumor multiplicity but not lung tumor incidence was significantly increased compared to the filtered air control group.

The Background Document for ETS notes that animals exposed to 'whole smoke' lost body weight during the first month of the experiment, but fails to stress the magnitude of the loss in body weight gain (ca. 20% during the first month, and roughly 15% reduction in body weight gain for the remaining exposure period.) Good Toxicological Practices (Montesano, et. al, 1986) should also have led to rejection of these study results due to overt toxicity in both the animal groups exposed to 'whole smoke' (significant reduction in average monthly body weight gain of 15-20% compared to the 'air control' mice) and 'filtered smoke' (significant, but lower, reduction in average monthly body weight gain compared to the 'air control' mice).

The Background Document for ETS neglects to mention important data presented for various smoke constituents in both the presented 'whole smoke' and 'filtered smoke' atmospheres. Witschi in his evaluation states:

> 'Based on the chamber concentrations of selected nitrosamines and polycyclic aromatic hydrocarbons, the possible maximum uptakes by the mice of NNK, NNN and benzo(a)pyrene during the 5 months

exposure period were three to six orders of magnitude below doses reported in the literature to produce 1 lung tumor in strain A/J mice. It was concluded that the gas phase of ETS is as carcinogenic as is full ETS.'

The Background Document devotes several pages to discussing the possible relevance of TSNA to the question of human carcinogenicity of ETS, but omits the data and conclusions cited above from their discussion of the Witschi results. Since TSNA are associated primarily with the particulate phase rather than the gas phase of smoke, there is a conflict between the importance placed by the Background Document for ETS on tobacco-specific nitrosamines as a significant class of biologically active compounds present in tobacco smoke and the Witschi studies. The discrepancy between the emphasis on TSNA by the Background Document and Witschi's data is even more striking when considering Witschi's last publication (Witschi et al., 1998); in this study A/J mice subjected to the above described "ETS" atmosphere did not respond to phenylethyl isothiocyanate, a compound shown to be anti-carcinogenic with NNK in the same paper.

Witschi et al. (1997b) hypothesized that the carcinogenicity of gas phase ETS may be due to some as yet unidentified, yet highly potent, carcinogens or by a substantial, possibly free radical-mediated, oxidative stress on the lungs. They concluded, however, that '*At present, there are no clues as to what constituent(s) of the gas phase of tobacco smoke are responsible for its tumorigenic action.*' Having made this statement Witschi et al. specifically listed the following five possible constituents of ETS as known animal and probable human carcinogens: benzene, formaldehyde, 1,3-butadiene, N-nitrosodimethylamine, and N-nitrosodiethylamine. Information regarding the carcinogenicity of these five compounds from government agencies and Witschi indicates that benzene is associated with increased risk of acute nonlymphocytic leukemia and other blood disorders, but not lung cancer in man (Federal Register Notice EPA/600/P-97/001A); that formaldehyde is considered to be a probable human carcinogen (EPA Group B1) although the evidence is considered to be 'limited' rather than sufficient for an increased risk of lung and nasopharyngeal cancer; that 1,3-butadiene is associated with increased risk of leukemia, but not lung cancer in man (Federal Register Notice EPA/600/P-98/001A); and that N-nitrosodimethylamine is primarily a liver and bile duct carcinogen in the rat (Peto et al, 1991) and N-nitrosodiethylamine induces primarily liver and esophageal tumors in rats (Peto et al., 1991). Exposure of rats by long-term inhalation of N-nitrosodimethylamine results mainly in nasal cavity tumors (Klein et al., 1991). N-Nitrosodimethylamine and N-nitrosodiethylamine seldom induce tumors of the lower respiratory tract and lung.

In conclusion, the NTP, since its inception in November 1978, has had the mandate to identify toxic chemicals that must be controlled to prevent human disease. For this purpose, the NTP has traditionally relied on standard 2-year bioassays in rats and mice of both sexes. According to the International Agency for Research on Cancer, the A/J mouse model cannot be considered to provide conclusive evidence for carcinogenicity in the absence of supporting data obtained from other animal species (Gart, et al., 1986). Although studies have been performed using both rats and mice, the Background Document for ETS selectively and solely considers assays in the highly variable A/J mouse strain in its analysis of ETS. The quality of the two studies claiming a carcinogenic response to ETS fails to meet standards set by the NTP, OECD, and Good Toxicological Practices. The

NTP has previously compared the response of the A/J mouse with animal strains routinely used by the NTP for bioassay purposes (Maronpot et al., 1986) and concluded:

> *'There was lack of congruity of results between the strain A pulmonary tumor bioassay and the 2-year rodent carcinogenicity bioassay.'*
>
> *'A lack of consistency in strain A bioassay results from two separate laboratories.'*
>
> *' Carcinogenicity test data are relevant only to the test model employed.'*

In the case of the A/J mouse model, induction of adenocarcinoma is the only biologically relevant effect, since small cell and squamous cell carcinomas have not been observed following exposure to any test agents. Thus, this bioassay model and its application to inhalation studies of 'environmental tobacco smoke' is only relevant to the induction of adenomas and adenocarcinomas in the A/J mouse, and is of uncertain mechanistic biological relevance to man. Although fairly reproducible in terms of increased lung tumor multiplicity, the overt toxicity seen as a loss of body weight during the inhalation period as well as the various mechanistic studies performed by Witschi, e.g., the failed modulation of tumor rates with known mouse lung carcinogens, the similarity in effects by filtered and unfiltered smoke, or the lack of inhibition by agents known to interfere with the carcinogenesis by NNK, seriously undermine the plausibility of this model and its use as a basis for regulatory decisions.

Interactions of cigarette smoke with known carcinogens

Finch et al. (1996) exposed female strain A/J mice to diluted mainstream smoke of the Kentucky 1R3 reference cigarette (248±33 mg TPM/m^3, 300 ppm CO) for 6 h/d, 5 d/wk for 26 weeks, with and without pretreatment using a single i.p. injection of 100 mg/kg NNK three days prior to smoke inhalation. Although the Background Document stresses that NNK induced lung tumors in mice at 26 weeks (19/20; 95%), no mention is made of the data showing that exposure to tobacco smoke failed to induce lung tumors (0/19 animals) and numerically lowered the tumor incidence in the NNK-treated mice (13/16;81%).

Mechanistic and Relevant Studies: Carcinogenicity of tobacco-specific carcinogens

NNN does not induce lung tumors in either the rat or the hamster (reviewed by IARC, 1986 and Hecht, Chem. Res. Toxicol., 1998; 11:559-603).

Mechanistic and Relevant Studies: Metabolism of tobacco-specific nitrosamines

Many of the statements in this section are clearly in conflict with published literature described in a previous Philip Morris NTP submission (PM, 1998a). Some of the errors in fact or interpretation are described below:

- 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), per se, does not form pyridyloxobutyl adducts with lung and liver DNA according to the cited publication (Peterson et al., 1991).

- One study reports that NNN/NNK-derived pyridyloxobutyl DNA adducts are present in higher levels in the peripheral lung of smokers than nonsmokers (Hecht et al., 1994). A second study by the U.S. NCI failed to detect the same adduct in lung tissues of smokers (Blomeke et al., 1996).

- The cited study by Hecht et al. (1993), which is also mentioned on page 11 of the Background Document for ETS, appears to be the only nitrosamine-related document actually used in preparation of the Background Document. Consequently, the chain of reasoning followed by Hecht is repeated with the same supporting references in the Background Document. In both cases these studies refer to biomonitoring of NNK metabolite excretion in smokers. However, neither the original reviewers of the manuscript submitted to the New England Journal of Medicine or the authors of the Background Document appear to have actually checked the calculations of the presented results. According to Hecht et al., ' The mean ($\pm$SD) amount of NNAL and NNAL glucuronide was significantly higher after exposure than at base line (33.9$\pm$20.0 vs. 8.4$\pm$11.2 ng per 24 hours [127$\pm$74 vs. 31$\pm$41 pmol per day], $P<0.001$) and was significantly correlated with urinary cotinine excretion (r-0.89, $P<0.001$).' The data actually calculate to show a mean ($\pm$SD) amount of NNAL and NNAL glucuronide at base line of 17.0$\pm$25.1 pmol per day which increases to 77.3$\pm$61.7 pmol per day after exposure. The statistical test used is not mentioned, and the level of significance is probably wrong due to incorrect calculation of the data.

Appendix 1. Concentrations of Compounds Associated with Mainstream and Sidestream Tobacco Smoke and Indoor Air Polluted with Tobacco Smoke

The appendix presents totally confusing and mixed data without any referenced source. Not only are data for smoke constituents presented, but also data for biomarkers or exposure (e.g., blood carboxyhemoglobin, plasma cotinine and thiocyanate, aromatic hydrocarbons and alkanes in exhalate, thioethers in urine). Some of the units used are incorrect (i.e., nicotine, office buildings measured in pg/m^2 min). The data do not originate from Claxton et al. (1989) mentioned in the footnote.

Appendix 2. The Genotoxicity of Compounds Associated with Environmental Tobacco Smoke

The appendix presents a selection of data for compounds claimed to be associated with ETS but lacking support evidence. Some of the compounds are present in ETS, but ETS is not their only source in indoor air (e.g., PAHs, benzene, formaldehyde, limonene, naphthalene, NDEA, NDMA, phenol). Inconsistent with other sections of the Background Document is the absence of NNK from this list of Compounds associated with ETS.

In summary, it is clear that the NTP background document on ETS does not present a complete, accurate, or balanced analysis of the relevant data. It has

failed to identify, much less review, a large part of the literature, including a large body of research on human exposure by Phillips and co-workers and the most recent IARC study. There are a number of inaccuracies; examples include the errors related to TSNA carcinogenicity and metabolism. In reports of epidemiological studies, the Background Document for ETS has frequently quoted results for only the highest reported level of exposure – sometimes appropriately defined as dose and sometimes simply defined as reported duration of exposure. With respect to the application of the Bradford Hill guidelines on epidemiological data, evaluation of the complete data set on reported ETS exposure and lung cancer demonstrates that the data are inconsistent, represent an extremely weak association, and are of questionable biological plausibility due to low exposure levels of individual components. Many available animal studies were not discussed in the Background Document, and those upon which an emphasis was placed utilized an experimental animal which had been previously rejected as unsuitable for carcinogenicity testing by the NTP.

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Comparison of NTP Diesel Exhaust and ETS Background Documents

Comparison of NTP Diesel Exhaust and ETS Background Documents

It seems clear that the data for ETS and the data for diesel exhaust were presented in an inconsistent manner in the respective NTP Background Documents. This lack of consistency may well explain the different classifications proposed for these two mixtures by NTP.

The purpose of this comment is to highlight significant inconsistencies in the NTP listing process for these two mixtures. In order to discuss the inconsistencies, it is necessary, obviously to refer in part to NTP's treatment of ETS. However, our discussion of NTP's decision-making with respect to ETS does not in any way express agreement with NTP's conclusions, determinations, or classification.

Results of Animal Testing Reviewed in the Two Background Documents

There are numerous similarities with respect to the data deemed by NTP to be relevant for diesel exhaust and ETS exposures regarding the possible human carcinogenicity of these two complex mixtures. NTP chose to rely on limited data for both compounds in animal testing. Based on animal data considered by NTP, diesel exhaust has been shown to be carcinogenic to the rat in a number of different laboratories, but positive results have not been consistently obtained in other animal models. Similarly, NTP selectively noted that sidestream smoke, used as a surrogate for ETS, has recently been reported by a single laboratory to statistically significantly increase the multiplicity of the spontaneous formation of lung tumors in the A/J mouse at extremely high doses. However, no statistically significant increase in the incidence of lung tumors was reported. Significantly, attempts to induce tumors in other animal models with either mainstream or sidestream smoke have repeatedly met with failure. It is quite possible that neither of these animal models is at all useful in predicting human responses for either diesel exhaust or ETS.

Epidemiological Results Reviewed in the Two Background Documents

The epidemiological results considered by NTP are similar for the two substances. A recent meta-analysis of 29 epidemiological studies investigating the possible association of diesel exhaust exposure with lung cancer (Bhatia, et al., 1998) reported a pooled relative risk of 1.33 (95% CI, 1.18-1.51). The often cited 1992 EPA risk assessment on ETS exposure (U.S. EPA, 1992) reported a pooled relative risk for 11 US studies of 1.19 (90% CI, 1.04-1.35). Given this striking similarity, it might have been anticipated that a scientific body attempting to determine the potential human carcinogenicity of the two substances would have arrived at identical classifications. However, this was not the case for the NTP. In the Board of Scientific Counselors Report on Carcinogens Subcommittee meeting of Dec. 2-3, it was recommended that ETS be classified as a "known human carcinogen," whereas the recommendation was that diesel exhaust particulates be classified as "reasonably anticipated to be a human carcinogen." Is it possible that different conclusions were reached by the NTP subcommittee based upon differences in the manner in which the two respective background documents presented the data? This analysis will explore this possibility.

Although the respective background documents provide considerable data on chemical composition of diesel exhaust and ETS, as well as animal testing data, it is clear that the NTP subcommittee relied almost exclusively on the reported epidemiological data in forming its opinion. Therefore, this comparison will be restricted to Section 3, Human Studies, for both background documents. Both documents are organized in the same manner. The first part is devoted to key summary analyses of the epidemiology, the second part to "current epidemiology studies," and the third part is a concluding discussion. Despite this similarity in organization, however, there are major differences between the two documents.

Section 3 of the ETS background document cites three summary reports; namely, IARC (1986), U.S. EPA (1992), and California EPA (CalEPA) (1997). The background document on diesel exhaust, however, cites a single report; namely, IARC (1989). Risk assessments have been prepared by both EPA and CalEPA on diesel exhaust as well; however, no reference was made to these two reports in the background document on diesel exhaust. NTP might argue that perhaps there is good reason for not referencing the EPA risk assessment on diesel exhaust, since it has never officially been issued. However, the lack of reference to the CalEPA risk assessment is difficult to understand. For example, in June 1998 the CalEPA Air Resources Board (California Environmental Protection Agency, 1998) identified diesel exhaust as a toxic air contaminant. The Air Resources Board proposed amending Titles 17 and 26 of the California Code of Regulations, Section 93000, to include diesel exhaust as a toxic air contaminant and recommended that no threshold limit can be established below which adverse health effects are not anticipated. This recommendation was based in part on the epidemiological studies published on diesel exhaust:

> The lung cancer findings are consistent and the association is unlikely to be due to chance. These epidemiological studies strongly suggest a causal relationship between occupational diesel exhaust exposure and lung cancer. (Appendix II, p. 4)

Given this relevant finding by the California EPA with respect to diesel exhaust, it is difficult to understand why this information was not included in NTP's background document.

A second major difference between the two documents is the manner in which recent epidemiological studies were summarized. For the diesel exhaust background document fourteen "recent" (six cohort and eight case-control) epidemiological studies were discussed, "recent" being defined as being published after the 1989 IARC report. Each discussion concluded with a brief summary of the strengths and weaknesses of the study. In almost every case, the background document pointed out that the study was limited by its lack of actual exposure data. Four of the case-control studies did provide at least a semi-quantitative measure of exposure, and three of these four studies reported statistically significant OR's at the highest level of exposure. Gustavsson, et al. (1990) reported an OR of 2.43 (95% CI, 1.32-4.47) for 10 cases at the highest level of exposure; Steenland, et al. (1998) reported an OR of 1.64 (95% CI, 1.09-2.49) for the highest quartile of exposure; while Swanson, et al. (1993) reported an OR of 2.5 (95% CI, 1.40-4.4) for drivers of heavy trucks for more than 20 years (121 cases). The NTP background document on diesel exhaust mentioned other weaknesses as well: lack of adjustment for possible confounding (a point raised for almost all of the studies) and the small number of cases on which certain studies based their risk estimates.

In contrast, the ETS background document discusses only four "recent" epidemiological studies, "recent" being defined as being published after the 1986 IARC report – one cohort study and three case-control studies. There is no suggestion that weaknesses, for example, lack of adjustment for confounding, are present in any of these studies. This is despite the fact that none of these studies actually measured ETS exposure, and that only two of the four adjusted in any way for confounding. We have described many of these weaknesses in some detail in our critique of the Draft Background Document for ETS, included in this submission.

Another major difference between the two documents is related to the conclusions. The diesel exhaust background document concludes with the following paragraph:

> In summary, DE exposure is associated with lung cancer in the majority of studies, with a (sic) overall relative risk of about 1.3. Some studies found dose-responses, with higher risks in the more heavily exposed groups. Although the risk is small, it is not readily explained by confounding by smoking or asbestos exposure. Most studies had little or no quantitative information on actual exposures, but the resulting misclassification would be more likely to disguise an effect than to produce a spurious one and may provide an explanation for the small size of the risk. (p. 35)

The ETS background document, on the other hand, concludes as follows:

> In summary, it appears unlikely that either confounding or other types of bias can account for the risk ascribed to ETS exposure. The consistency of risks observed across individual studies conducted with various populations and methodologies, the presence of an exposure-relationship in many studies, and the biological plausibility of the relationship all argue strongly that the association of ETS exposure with lung cancer is causal.

The major difference between these two conclusions is that the ETS background document clearly adopts the conclusion that the association between ETS exposure and lung cancer is causal, but the diesel exhaust background document fails to reach that conclusion. According to NTP, epidemiological studies for both substances show an apparent weak association – 1.3 for diesel exhaust and 1.19 for ETS (U.S. EPA, 1992). Further, according to NTP, epidemiological studies for both substances reported dose-response relationships. Under NTP's analysis, results for both substances were equally consistent – or inconsistent depending on how one views the data. Lastly, there is no NTP argument from the perspective of biological plausibility which accounts for the difference in classification between ETS and diesel exhaust.

Discussion at the December 2 - 3 Meeting

With some striking inconsistencies regarding the manner in which NTP reviewed the epidemiology of diesel exhaust and ETS having been identified, the question remains: is there any indication that these differences in any way influenced the decisions that NTP reached regarding these two substances? An examination of the transcript of the NTP Dec. 3 discussion of diesel exhaust makes

it clear that this may indeed have been the case. Two quotations illustrate this point. The first is by Dr. Belinsky:

> Just a comment again to comment on the epi data with diesel versus ETS: I mean, the confidence intervals on a lot of these epi diesel studies were very large, going down to .7 and extending. And with the ETS they were much, much tighter.

This comment is a reflection of the fact that NTP provided data for 14 studies on diesel exhaust and only four studies for ETS. Had 14 "recent" ETS studies been discussed, equally wide confidence intervals would have been observed. The second comment is by Dr. Frederick:

> Cogent to the question, I am not at all convinced that we do a good job of controlling for smoking in a group like truck drivers, because I have to think that long hours in a cab in tightly controlled conditions, I am not entirely convinced that we have got ways of sorting out the effect of these things. And it is at least, you know, casual experience, a group that does an awful lot of smoking.

Dr. Frederick's comments refer, of course, to the possibility that active smoking could have confounded the reported association between diesel exhaust exposure and lung cancer. Certainly NTP viewed this as a potential concern, and consequently the NTP document carefully pointed out that many of the studies had not corrected the reported odds ratios or relative risks for smoking. This is despite the fact, however, that the conclusions stated that, "[A]lthough the risk is small, it is not readily explained by confounding by smoking or asbestos exposure." The ETS background document, on the other hand, bases its conclusion that confounding has been adequately corrected for in the epidemiology of ETS and lung cancer on a single study (Fontham, et al., 1994). This is despite the fact that a careful analysis of all of the data suggests that confounding can account for some part, although probably not all, of the risk.

In conclusion there seems to be clear evidence that the data for ETS and diesel exhaust were not presented at all consistently by their respective background documents, and that this lack of consistency may well explain the different classifications given to these two mixtures.

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Analysis of Epidemiological Claims of James Repace

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The material that Mr. James Repace presented at the NTP Board of Scientific Counselors Report on Carcinogens Subcommittee meeting of Dec. 2, 1998, regarding ETS included the claim that "when [the relative risks for ETS exposure and lung cancer] are corrected for background ETS in the control group, the adjusted odds ratio is better than 2. In fact, I would place it at 2.5." (meeting transcript, p. 203) Mr. Repace briefly mentioned two pieces of evidence that allegedly support this assertion. The first is one of his publications that he indicated was contained in his submission to NTP, and this will be discussed in considerable detail below. The second was a chart based on a table in the 1979 Surgeon General's report (U.S. Dept. of HEW, 1979; see attachment 1) that suggested that smokers who did not inhale had one-half the incidence of lung cancer of smokers who inhaled deeply. (Mr. Repace stated that about two-thirds of the risks of smokers who don't inhale "seems to be coming from ETS", but an examination of the data in the report do not substantiate that conclusion.) The Surgeon General's report, while characterizing inhalation as the "major mechanism whereby lung tissue is exposed", did not propose that these data yielded any information on ETS exposure. The only comments on this in the Surgeon General's report included a restatement of the reported excess risk for smokers relative to non-smokers and the suggestion that "cigarette smokers may underestimate the degree to which they inhale cigarette smoke."

The publication to which Mr. Repace referred in his NTP presentation was published in 1985 (Repace and Lowrey, 1985). In that publication the authors develop a quantitative assessment of nonsmokers' risk of lung cancer. Flaws in that assessment are demonstrated below. Repace and Lowrey contend that there are 4700 excess deaths from lung cancer per year from ETS exposure for the 62.4 million US nonsmokers aged >35 years, and that the excess risk of lung cancer can be related to the inhaled dose of ETS-derived RSP, with 5 excess deaths from lung cancer/100,000 population resulting from inhalation of 1 mg ETS-derived RSP per day. In order to arrive at these conclusions, Repace and Lowrey had to assume a relative risk for non-smoker lung cancer, and although that relative risk was never specifically reported in the 1985 publication, the data presented can be utilized to calculate it. When this is done with the Repace contentions and assumptions, the relative risk turns out to be 2.2, or, a value greater than 2, as Mr. Repace suggested in his presentation to the NTP. This relative risk, of course, is considerably greater than risks reported in most individual epidemiological studies and any summary relative risk obtained by meta-analysis of all of the collected epidemiological studies on estimated ETS exposure and lung cancer. Specifically, for example, it is 6-times greater than the often cited EPA (U.S. EPA, 1992) meta-analysis of 11 US studies. Mr. Repace has claimed that the fact that all of the published epidemiological studies have used control groups that had also been exposed to ETS explains why these pooled relative risks are so low. To evaluate the accuracy of Mr. Repace's conclusion, it is essential to document the derivation of the relative risk that he uses in his models.

The 1985 Repace and Lowrey publication utilizes information published by Phillips, et al. in 1980 to arrive at the relative risk used in their analyses (Phillips, et al. 1980a; Phillips, et al. 1980b). These authors analyzed health data obtained

from non-smoking Seventh-Day Adventists (SDA) and non-smoking non-SDA in order to determine if differences between the two groups existed with respect to certain health end-points. They reported that the ratio for age-adjusted mortality rates for lung cancer comparing non-smoking SDA to non-smoking non-SDA was 0.42 for females (statistically significant with $p<0.01$) and 0.67 for males (not statistically significant). The authors suggest that the most likely explanations of these results are consequences of the lifestyle differences between SDA and non-SDA. One aspect of that lifestyle difference may be exposure to ETS. However, there are numerous other differences which are acknowledged but not considered by Repace and Lowrey. For example, Phillips, et al. (1980a) point out that:

> By Church proscription, virtually all SDA abstain from the use of tobacco and alcohol, and a large majority adhere to one or more of the recommendations of the Church regarding other health habits and practices that are advocated primarily for their established or supposed health-promoting effects. Presently, about 54% of SDA follow a vegetarian diet that includes milk and eggs, and 41% rarely or never use caffeine-containing beverages. They also tend to abstain from sweets, other highly refined foods, hot condiments and spices. Regularity in vigorous exercise, adequate rest, and conservative social mores are strongly encouraged.

As a consequence, Repace's and Lowrey's attribution of the reported difference in risk between non-smoking SDA and non-smoking non-SDA to ETS exposure is not justifiable. While it is highly likely that SDA are not significantly exposed to ETS in the home, results of Phillips and co-workers cited by Repace and Lowrey indicate that less than half of the SDAs work in environments which are not likely to permit smoking (i.e., SDA owned and operated organizations). Therefore, it is not at all obvious that Repace's and Lowrey's assumption that SDA would be a non-exposed control group is correct.

If the difference in lung cancer incidence between non-smoking SDA and non-smoking non-SDA were due to multiple differences in life style, and not simply ETS exposure, then one might expect to see differences in other diseases not related to either active smoking or ETS exposure. Therefore, it is quite instructive to look at the difference between the two groups that Phillips, et al. reported for colon-rectal cancer, a cancer unrelated to any form of tobacco smoke exposure. For females the ratio was 0.56 (statistically significant with $p<0.1$) and for males the ratio was a 0.67 (not statistically significant.) The observed differences for colon-rectal cancer, if real, must be attributable to lifestyle differences unrelated to ETS exposure. These ratios are extremely close to those reported for lung cancer, strongly suggesting that life style factors other than ETS exposure are likely to account for these reported results as well.

It is also extremely instructive to examine the data in Phillips, et al. for coronary heart disease. For women, the ratio of non-smoking SDA to non-smoking non-SDA was 1.01; that is, for women there was absolutely no difference between the two groups. In other words, no risk for coronary heart disease is observed when what is claimed to be a control group unexposed to ETS is used to determine the risk associated with exposure to ETS. A difference for coronary heart disease for men between non-smoking SDA and non-smoking non-SDA is observed, with the ratio being a statistically significant 0.76. However, once again, it is highly likely that the observed difference can be attributed to differences in lifestyle related to

diet and physical exercise between SDA and non-SDA . Consequently, there is no justification for Mr. Repace's claim that if an unexposed control group is used, the relative risk for the association of ETS exposure with lung cancer would be greater than 2.

The flaws in Mr. Repace's claim are manifold. First of all, the claim is based on published studies by Phillips, et al. that were in no way designed to investigate the health effects of ETS exposure. Secondly, as Phillips, et al. point out, there are numerous lifestyle differences between SDA and non-SDA other than simply ETS exposure. Thirdly, the data Phillips, et al. report for the differences between non-smoking SDA and non-smoking non-SDA give results for colon-rectal cancer, a form of cancer unrelated to tobacco use, similar to those for lung cancer. Finally, no difference is observed for coronary heart disease in women for the two groups, suggesting that if Mr. Repace wished to claim that the data from Phillips, et al, establish a certain association between ETS exposure and lung cancer, he should acknowledge that the same study suggested no association between ETS exposure and coronary heart disease in women.

In Repace and Lowrey's 1985 publication they claim to have substantiated their model by carrying out a calculation to show that their methodology gives results in complete agreement with the 1981 Garfinkel prospective study on ETS exposure and lung cancer (Garfinkel, 1981). This would appear on the surface to be quite difficult given that Garfinkel reported a relative risk of 1.27 for women married to husbands who smoked less than 20 cigarettes per day and a relative risk of 1.10 for women married to husbands who smoked greater than or equal to 20 cigarettes per day. Repace and Lowrey construct the following model. They claim that a certain percentage of the controls (and cases) were exposed to ETS at work, and that therefore Garfinkel's results appear to be low since he is comparing an exposed case group to a partially exposed control group. They therefore use their model to adjust for this alleged error.

Repace and Lowrey start with a base age-adjusted lung cancer mortality rate for non-smoking women of 8.7. This value is taken, perhaps inappropriately, from the Hirayama study (Hirayama, 1981), despite the fact that lung cancer mortality in Japan is quite different from lung cancer mortality in the US. They apply a correction to what they term "tainted controls;" that is, controls that were not exposed to ETS in the home but were exposed at work. In order to do this Repace and Lowrey first estimate the percentage of females in the workplace. Their estimate of 38% appears to be quite reasonable from the data given. They then assume that 100% of these working women were exposed at work ("[t]hus, it appears that about 38% of the women in this study were in the labor force, and presumably exposed to passive smoking while at work" (Repace and Lowrey, 1985, p. 10)). Next they claim to calculate the ETS associated lung cancer mortality from workplace exposure and home exposure using a relative risk of 2.2; that is, 5 excess lung cancer deaths per 100,000 per year per mg of ETS-derived RSP inhaled. In order to do this, it was necessary for Repace and Lowrey to calculate the level of ETS in both the home and the workplace. Utilizing their models, they estimated that a typical non-smoker in the home is exposed to an average inhaled dose of 0.45 mg/day, while a typical non-smoker in the workplace is exposed to an average of 1.8 mg/day. In other words, they contend that exposure at work is four-fold greater than exposure at home.

Repace and Lowrey's resolution of their results with those of Garfinkel (1981) can now be reconstructed. The rate for the true controls in the Garfinkel study is 8.7, which, as noted above, is derived from Japanese base lung cancer death rate. The rate for the tainted controls, that is those controls who were not truly controls because of workplace exposure, is 17.8. This number is derived from Repace and Lowrey's calculation of 5 lung cancer deaths per 100,000 person years for every mg of ETS exposure per day, which in turn is based on a relative risk of 2.2 for lung cancer associated with ETS exposure. Therefore, the tainted controls have a lung cancer rate (base plus ETS exposure) of

8.7 + (1.82 mg/day workplace exposure X 5 lung cancer deaths per 100,000 person years per mg ETS exposure per day) = 8.7 + 9.1 or 17.8.

The weighted rate for the controls is then

{8.7 X 62% (the percentage of women not in the workforce)} + {17.8 X 38% (the percentage of women in the workforce)} = 5.40 + 6.76 = 12.16.

The same calculation must then be carried out for the exposed group. Exposed workers have a base rate of 20.05. This is obtained from the sum of 8.7, the unexposed base rate, plus 9.1, the excess rate due to workplace exposure, plus 2.25, obtained by multiplying household exposure (0.45 mg) by the rate of 5 lung cancer deaths per 100,000 person years per mg ETS exposure per day. Exposed non-workers have a rate of 10.95, the base rate of 8.7 plus the increase in rate due to household exposure of 2.25. The weighted rate is then

(10.95 x 62%) + (20.05 X 38%) = 6.79 + 7.62 = 14.41.

Repace and Lowrey then divide 14.41 by 12.16 to obtain 1.19, almost exactly the overall relative risk obtained by Garfinkel of 1.20. Moreover, the lung cancer death rate for the weighted average of the "exposed" and "control" categories is 13.8 per 100,000. If Repace's and Lowrey's contentions and assumptions are accepted, this calculation is in agreement with the rate of 13.3 per 100,000 reported by Garfinkel over the 12 years of his study. This, they state, is proof of the veracity of their methodology and, they claim, confirms the RR of 2.2 for ETS exposure and lung cancer when a true non-exposed group is used as a control group. The calculation is shown in tabular form in Table 1.

Table 1
Repace and Lowrey's Reproduction of the Garfinkel (1981) Relative Risk and Lung Cancer Death Rate Using Their Model (1985)

Group	Rate
True Controls	8.7
"Tainted" Controls	17.8 (8.7 + 9.1)
All Controls (Weighted Mean)	12.16
Exposed Workers	20.05 (8.7 + 2.25 + 9.10)
Exposed Non-Workers	10.95 (8.7 + 2.25)
All Exposed (Weighted Mean)	14.41
Calculated Relative Risk	14.41/12.16 = 1.19
Calculated Death Rate	13.8 per 100,000

As can be seen from the above analysis, this calculation rests on numerous assumptions. It is essential, therefore, to examine these assumptions carefully to determine if Repace and Lowrey have actually made the best possible assumptions. Our discussion of the assumptions that underlie the Repace and Lowrey model, and the presentation of numerical values derived from their model using different assumptions, in no way implies agreement with the assumptions, the model, conclusions or claims derived from it, or the hypothesized association between ETS exposure and lung cancer.

The first assumption is the base rate for lung cancer. As pointed out above, Repace and Lowrey chose a value of 8.7 taken from Hirayama. However, a value more consistent with their own hypotheses would be the adjusted lung cancer mortality rate for female SDA which is 9.4. Even this value is likely to be lower than a hypothetical group unexposed to ETS as a consequence of other lifestyle differences between SDA and the general population, as was pointed out above. The next assumption was that of the 38% of women in the workplace, 100% of these women would have been exposed to ETS. This assumption appears to be somewhat of an exaggeration, and in fact the Repace and Lowrey 1985 publication gives a very different percentage in a later section ("Appendix A1 estimates that nonsmoking U.S. workers are exposed on the job to tobacco smoke with a probability of 62%" Repace and Lowrey, 1985, p. 13). Therefore, a more consistent estimate for exposure to workplace smoking would be 62%, not 100%. Lastly, it is essential to determine whether Repace's and Lowrey's assumption of a four-fold difference for workplace exposure as compared to household exposure is valid. Repace and Lowrey themselves ask the question as to whether the numbers calculated for workplace exposure (1.82 mg/day) and for home exposure (0.45 mg/day) "are reasonable in terms of measurements of ambient tobacco smoke under natural conditions" (Repace and Lowrey, 1985, p. 15). They cite two different studies to confirm these differences. The first is a study by Repace and Lowrey (Repace and Lowrey, 1980; Repace and Lowrey, 1982) carried out in workplaces in Washington, D. C., between 1979 and 1980 which reported ranges of "ambient tobacco smoke" (particulate) ranging from 100 $\mu g/m^3$ to 1000 $\mu g/m^3$ with an average of all values of 242 $\mu g/m^3$. They contend that breathing of 242 $\mu g/m^3$ of ambient tobacco smoke for 8 hr at a rate of 0.99 m^3 h yields a daily average of 1.92 mg, which they consider to be reasonably close to their calculated value of 1.82 mg. Their claimed confirmation of household ETS exposure is derived from a study published by Dockery and Spengler (Dockery and Spengler, 1981a) where a 24-hour average of 19 $\mu g/m^3$ was found for households with a single smoker. When this number is used in Repace and Lowrey's model in order to adjust for air-exchanges, time in the home, and respiration rate, the value of the calculated exposure is 0.45 mg/day.

The use of two separate studies – one to confirm the model calculation for workplace exposure and one to confirm the model calculation for household exposure – is extremely unusual, particularly as Dockery and Spengler measured a level of workplace exposure. They cite a level of exposure to ETS particulate matter in the workplace of 20 $\mu g/m^3$ for each smoker present (Dockery and Spengler, 1981b). This number is essentially equal to the level they cite for the household. Given the fact that Repace and Lowrey (1985, p. 13) assume that working women spend three times as much time at home as at the workplace, we will make the conservative assumption that the two sources of exposure are equal,

meaning that the average woman, who is exposed at all, is exposed to the ETS from three smokers at the workplace.

The substitution of a value of 0.45 mg ETS-derived RSP per day workplace exposure for the 1.82 mg ETS-derived RSP changes not only Repace's adjustment for controls in his effort to reproduce the Garfinkel relative risk, but also changes Repace and Lowrey's calculation of five additional lung cancer deaths per 100,000 person-year-mg ETS-derived RSP/day. Repace and Lowrey had based this calculation on an average exposure of 1.43 mg ETS-derived RSP/day (Repace and Lowrey, 1985, p. 5). This number now becomes 0.56 mg ETS-derived RSP/day, leading to an assumption of an excess number of lung cancer deaths per 100,000 person-year-mg ETS-derived RSP/day of 13.2 (7.4/0.56; see Repace and Lowrey, 1985, p. 9). We can now reproduce the calculation which uses the Repace and Lowrey model to generate a value to compare with Garfinkel's reported relative risk and lung cancer death rate. This is shown in Table 2.

Table 2
Recalculation of Repace and Lowrey's Generation of the Garfinkel (1981) Relative Risk and Lung Cancer Death Rate Using Their Model (1985) with Alternative Assumptions

Group	Rate
True Controls	9.4
"Tainted" Controls	15.34 (9.4 + 5.94[13.2X0.45])
All Controls (Weighted Mean)	10.78
Exposed Workers	21.28 (9.4 + 5.94 + 5.94)
Exposed Non-Workers	15.34 (9.4 + 5.94)
All Exposed (Weighted Mean)	16.74
Calculated Relative Risk	16.74/10.78 = 1.55
Calculated Death Rate	15.1 per 100,000

The results of Table 2 are not at all in good agreement with the reported results of Garfinkel. The difference in excess risk between the Repace model (0.55) and the Garfinkel results (0.20) is 175%. The difference in lung cancer risk is considerably less, being only 13%.

Repace has continued to use his model, with the same major assumptions, to develop a methodology that can predict excess lung cancer rates by simply obtaining a salivary cotinine level (Repace et al., 1998). In extending his methodology he makes numerous other assumptions, many of which are as subject to dismissal after careful examination as the assumptions discussed above. In his 1998 publication he contends that his model can be validated by comparing his calculated data with measurements reported by Hammond, et al. (Hammond et al., 1995). However, the comparison he makes with the Hammond data may not be appropriate in that he is comparing data using fixed monitoring with a model which utilizes inhaled RSP or nicotine.

In summary, Mr. Repace has developed a series of complicated models all of which stem from an assumption that the relative risk for lung cancer associated with exposure to ETS is about 2.2. This assumption has been shown to be completely unwarranted. Claims by Repace that his models can be verified by

comparison to existing data are generally based on inappropriate assumptions regarding certain parameters in his models, and careful analysis of his work can demonstrate this. That these models readily appear to give results in terms of excess attributable deaths that are in at least order-of-magnitude agreement with other estimates (U.S. EPA, 1992) is a result of the fact that Repace has grossly overstated the risk but has also grossly overstated the exposure.

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Attachment 1
Table 4 from Section 5 of the 1979 Surgeon's General Report (p. 5-15)

Study	Degree of Inhalation	Mortality Ratio
ACS 25-State Study	Nonsmoker	1.00
	None	8.00
	Slight	8.92
	Moderate	13.08
	Deep	17.00
Swedish males	Nonsmoker	1.00
	None	3.7
	Light inhalation	7.8
	Deep inhalation	9.20